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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/588,555

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Allan Svendsen

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EXAMINER

SWOPE, SHERIDAN

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

10/28/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/588,555	Applicant(s) SVENDSEN ET AL.	
	Examiner SHERIDAN SWOPE	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-28,33 and 38-46 is/are pending in the application.
- 4a) Of the above claim(s) 17,19-26,28,40 and 42-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15,16,18,27,33,38,39 and 41 is/are rejected.
- 7) ☒ Claim(s) 15,16,18,27,33,38,39 and 41 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04 August 2006 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>0806</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's election, without traverse, of Invention I and modification H¹⁴⁴R in their response of July 29, 2008 is acknowledged. The elected invention is directed to an RP-II protease variant of SEQ ID NO: 2 having a H¹⁴⁴R substitution. It is acknowledged that, with the response of July 29, 2008, Claims 29-32 and 34-37 were cancelled, Claims 15, 18, 21-24, and 26 were amended, and Claims 38-46 were added. Claims 15-28, 33, and 38-46 are pending. Claims 17, 19-26, 28, 40, and 42-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 15, 16, 18, 27, 33, 38, 39, and 41 are hereby examined.

Priority

The priority date granted for the instant invention is March 31, 2004, the filing date of US 60/558,191, which disclosed the elected invention.

Title

The title should be amended to be descriptive of the elected invention.

Abstract

The abstract is objected to for "pro-tease", which should be "protease".

Drawings

Figures 1 and 2 are objected to for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO:). The sequence rules embrace all nucleotide sequences with ten or more bases and all amino acid sequences with four or more amino acids. Said sequences must be disclosed in a sequence listing and identified by a specific SEQ ID NO: (MPEP 2421.02). 37 CFR 1.821(d) requires the use of the assigned sequence identifier number

Art Unit: 1652

in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims of an application. Applicant is required to check the disclosure completely and to make corrections to identify all of the sequences disclosed therein by sequence identifier numbers.

Specification-Objections

The specification is objected to for containing hyperlinks. USPTO policy does not permit the USPTO, i.e, via an issued patent, to refer to any commercial sites, since the USPTO exercises no control over the organization, views or accuracy of the information contained on these outside sites. Hyperlinks and other forms of browser-executable code, especially commercial site URLs, are not to be included in a patent application. (MPEP 608.01) The specification should be carefully checked and all URLs removed.

Claims-Objections

Claims 15, 16, 18, 27, 38, 39, and 41 are objected to for reciting non-elected subject matter.

Claims 15 and 38 are objected to for poor grammar. In said claims, the phrase “at a distance of...to the ion-binding site” would be better stated as “at a distance of...from the ion-binding site”.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Art Unit: 1652

Utility

Claims 15, 16, 18, 27, 33, 38, 39, and 41 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The variant of SEQ ID NO: 2 having a H¹⁴⁴R substitution is likely to occur in nature. Therefore, the recited subject matter fails to show the “hand of man”. It is suggested that the term “isolated” or “recombinant” be used.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 18, 27, and 33, 39, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claim 16, the phrase “where the positions refer to BLC or corresponding positions” renders the claim indefinite. It is unclear what is being claimed; the skilled artisan would not know the metes and bounds of the recited invention.

For Claim 18, the phrase “144 and or 161” renders the claim indefinite. It is unclear whether said phrase means “144 and 161”, “144 or 161” or “144 and/or 161”. The skilled artisan would not know the metes and bounds of the recited invention.

For Claims 18, 39, and 41, reference to a specific amino acid position(s), without reference to a specific sequence, renders the claim indefinite. The skilled artisan would not know the metes and bounds of the recited invention.

Art Unit: 1652

For Claim 33, the phrase “produced in claim 15” renders the claim indefinite for the following reasons. First, a claim does not produce a product, a method produces a product. Second, Claim 15 is not a method claim.

For Claim 39, the phrase “the modification is...of BLC” renders the claim indefinite. It is unclear whether the variant is a BLC variant comprising the recited modifications or any RP-II protease variant comprising said modifications.

For Claim 41, the phrase “the modification is...of BLC” renders the claim indefinite. It is unclear whether the variant is a BLC variant consisting of only the recited modifications or any RP-II protease variant consisting of said modifications.

Claims 27 and 33 are rendered indefinite for improper antecedent usage as follows.

For Claim 27, “The RP-II protease of claim 15” lacks antecedent basis.

For Claim 33, the phrase “a RP-II protease variant...in claim 15” should be corrected to “the RP-II protease variant...in claim 15”.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 15, 16, 18, 27, 33, 38, 39, and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 2 having a H¹⁴⁴R substitution, does not reasonably provide enablement for any variant of any RP-II protease comprising any modification(s) within 10 angstroms of the ion-binding site. The specification

Art Unit: 1652

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 15, 16, 18, 27, 33, 38, 39, and 41 are so broad as to encompass any variant of any RP-II protease comprising modification(s) within 10 angstroms, or 6 angstroms, of the ion-binding site, wherein the variant has any or no activity. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed

Art Unit: 1652

knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to SEQ ID NO: 2 having a H¹⁴⁴R substitution.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galys et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Moreover, the claim fails to recite any function for the encompassed variants and, thus, the skilled artisan is not enabled for testing for the desired activity or using the encompassed variants.

The specification does not support the broad scope of Claims 15, 16, 18, 27, 33, 38, 39, and 41, which encompasses any variant of any RP-II protease comprising modification(s) within 10 angstroms, or 6 angstroms, of the ion-binding site, wherein the variant has any or no activity. The specification does not support the broad scope of Claims 15, 16, 18, 27, 33, 38, 39, and 41 because the specification does not establish: (A) the desired activity for all encompassed variants; (B) methods to test the encompassed variants for the desired activities; (C) how to use the encompassed variants; (D) the residues that make up the ion-binding site in all RP-II proteases; (E) regions of the protein structure which may be modified without affecting the desired activity; (F) the general tolerance of the desired activity to modification and extent of such tolerance; (G) a rational and predictable scheme for modifying any residues with an

Art Unit: 1652

expectation of obtaining the desired biological function; and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of any variants of any RP-II protease comprising any modification(s) within 10 angstroms of the ion-binding site, wherein the variant has any or no activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Written Description

Claims 15, 16, 18, 27, 33, 38, 39, and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of variant protein molecules encompassing any variant of any RP-II protease comprising modification(s) within 10 angstroms, or 6 angstroms, of the ion-binding site, wherein the variant has any or no activity. The specification teaches the structure of only a few representative species of said variant protein molecules and all are derived from a single parent protease.

Art Unit: 1652

Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than being a variant of any RP-II protease comprising modification(s) within 10 angstroms, or 6 angstroms, of the ion-binding site. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 15, 16, 18, 27, 33, 38, 39, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Norregaard-Madsen et al, 2001 (IDS). Norregaard-Madsen et al teach variants of RP-II proteases, including BCL, wherein the variants have at least 60% homology to the parent sequence or are encoded by a polynucleotide that hybridizes to the parent polynucleotide under very low stringency conditions (pg 17, parag 2 to pg 19, parag 1). The skilled artisan would believe that, more likely than not, said variants of Norregaard-Madsen et al encompass variants of any RP-II protease comprising modification(s) within 10 angstroms, or 6 angstroms, of the

Art Unit: 1652

ion-binding site. Therefore, Claims 15, 16, 18, 27, 33, 38, 39, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Norregaard-Madsen et al, 2001.

Claims 15, 16, 18, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Sloma et al, 1990. Sloma et al teach a protease having an Asp substitution at the position corresponding to His¹⁴⁴ of SEQ ID NO: 2. Therefore, Claims 15, 16, 18, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Sloma et al, 1990.

Claims 15, 16, 18, 38, and 39 are rejected under 35 U.S.C. 102(a&e) as being anticipated by Ostergaard et al, 2003 (filing date 17-APR-2000). Ostergaard et al teach a protease having a Met substitution at the position corresponding to His¹⁴⁴ of SEQ ID NO: 2. Therefore, Claims 15, 16, 18, 38, and 39 are rejected under 35 U.S.C. 102(a&e) as being anticipated by Ostergaard et al, 2003.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Art Unit: 1652

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943.

The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652